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A CASE-CONTROL STUDY OF CANCER OF THE ESOPHAGUS AND GASTRIC CARDIA IN LINXIAN

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A case-control study involving interviews with 1,244 patients (758 males and 486 females) with cancer of the esophagus or gastric cardia and 1,314 population-based controls (789 males, 525 females) was carried out in Linxian, a rural county in North Central China with one of the world's highest mortality rates for these tumors. Cancer risks tended to rise with increasing intake of wheat and corn, but no association was found with adult intake of pickled vegetables, the leading *a priori* suspect, and risks were not elevated among those consuming low quantities of fresh vegetables or fruits. Few differences in preparation or storage of food or water were detected, although cancer patients reported less fluid intake than controls. Few persons reported drinking alcoholic beverages. Smoking was reported by 61% of the male cases and was a mild risk factor, related more to cancer of the cardia than of the esophagus. The risk was increased by 70% among those whose parents had esophageal or stomach cancer, but only slightly among those whose spouses had such cancers, suggesting that exposure early in life and/or genetic effects may be involved.

The nationwide survey of mortality in 1973–75 conducted by the Cancer Institute of the Chinese Academy of Medical Sciences identified esophageal cancer (EC) as the second leading cause of death from cancer in China, accounting for 27% of all cancer deaths in men and 20% in women (NCCO, 1980*a*). The survey showed remarkable geographic variation across the country, with the most prominent cluster of elevated rates seen in North Central China, particularly in the Taiheng mountain area on the border of Henan, Hubei and Shanxi Provinces. Located in this area is Linxian, a county of 800,000 persons where the age-adjusted rates of esophageal cancer mortality per 10^5 were 161 in males and 103 in females during 1973–75, exceeding the national levels by nearly 10-fold (NCCO, 1980*b*). Historical data are limited, but it appears that esophageal cancer has been a problem in the area for many years and that age-adjusted death rates have changed little from 1959 to 1981, although there has recently been some evidence of a decline in younger age groups (Li, 1982; Lu *et al.*, 1985).

Previous studies of esophageal cancer in Linxian and other high-risk areas of China suggested several etiologic clues, but no conclusive associations to account for the geographic clusters of this cancer (Li, 1982; Yang, 1980; CGR, 1975; Li *et al.*, 1980). The high-risk areas are generally rural and poor, with infertile soils and inadequate water supplies. Diets typically have been low in fruits, vegetables and animal foods, with deficiencies of minerals and vitamins, particularly riboflavin (Muñoz *et al.*, 1982; Yang *et al.*, 1982; Thurnham *et al.*, 1985). Some specific foods commonly eaten in Linxian may be involved. Most attention has focused on foods that are eaten fermented or moldy, particularly an unusual local variety of pickled vegetables. Pickled vegetables in Linxian are made by fermenting turnips, sweet potato leaves, or other vegetables in water without salt or vinegar. Extracts of these pickled vegetables are mutagenic and contain benzopyrenes and N-nitroso compounds (Lu *et al.*, 1981; Li, 1981; Li and Cheng, 1986). Fungal contamination (particularly from *Fusarium moniliforme*), nitrosamines derived from other sources, and silica fragments from ingested millet have also been suggested as possible risk factors (Li and Cheng, 1986; Singer *et al.*, 1986; O'Neill *et al.*, 1982). Smoking and drinking, the major determinants of esophageal cancer in Western societies, have not been thought to be key risk factors in China. Familial clustering has been observed in some high-rate areas (Li and He, 1985), but environmental factors are thought to be responsible for most of the geographic clustering.

To investigate determinants of the high rates of esophageal cancer in Linxian, we conducted a large population-based case-control study. The investigation was begun after a pilot study (Li *et al.*, 1985) demonstrated an efficient system for rapid identification of cases (with interviews typically conducted within 2 weeks of diagnosis), a high interview completion rate (>97%), and an acceptable heterogeneity of exposures for a number of items (including pickled vegetable intake) within the study population.

MATERIAL AND METHODS

Identification of patients and controls

All diagnoses of esophageal cancer occurring over a 21-month period (April 1984–December 1985) among residents of Linxian aged 35–64 years were identified from all hospitals in the county, using an existing reporting system (the Linxian Cancer Registry) to aid in the ascertainment of cases. Cases and controls were limited to the age-group 35–64 years because there were few EC cases among persons below age 35 and because it was anticipated *a priori* that persons 65 and over might be reluctant to be interviewed and might not have as accurate a diagnosis of EC.

Diagnostic material for all cancer patients was reviewed by a panel of clinicians, radiologists and pathologists. The review indicated that for many patients the tumors occurred in the esophageal-gastric junction or gastric cardia. These were included as cases, since they would have been listed as having "esophageal" cancer under the reporting systems used over the past 25 years in Linxian, where cardiac and esophageal cancers historically have been thought of as a single clinical entity.

Controls were randomly selected from all individuals in the Linxian population of similar age and sex but without cancer. We developed the following scheme for the sampling of individuals. To obtain a control in a specific sex and age category (*e.g.*, a male 40–45 years old), we used a random number table to select a commune from among the 15 in Linxian, weighting according to the numbers of men in the age group who were counted in a recent census of Linxian. Next, a brigade (subunit of commune) was randomly chosen from among those in the commune, again with the brigade's probability of selection proportional to the population in the sex-age group for that brigade. We then visited the brigade office and randomly selected a team, weighting according to its total population (the age distributions of the teams are not readily known but are

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generally similar within brigades). Each brigade office maintains a book listing all residents of each team. We then consulted the book for the team selected to identify all men aged 40–45 years, one of whom was randomly selected as the control. This process was repeated for each control.

Data collected

Patients and controls were interviewed by trained interviewers using a structured questionnaire. The questionnaire obtained detailed information on residence, occupation, smoking, diet, food preparation and storage methods, beverage consumption, body size, medical conditions and family medical history. An extensive dietary section of the questionnaire with 72 food items inquired about nearly every common food in the Linxian diet. Questions about food and beverage intake, as well as income, smoking and water supply, referred to 2 time periods: the late 1950's, and the late 1970's. The late 1970's were chosen as a recent time period assumed to precede symptomatic disease, while the late 1950's were chosen as the time before local agricultural practices and water usage patterns became permanently altered by the completion of the Red Flag Canal, an extensive county-wide irrigation system.

Data processing and analysis

Data were manually edited in Linxian, then transcribed onto coding sheets for computerization in the United States. The answers to all food frequency questions were converted into a common unit of times eaten per year. The frequencies for the individual food items, as well as for foods grouped into several classes, were then categorized according to the distributions of intake among the controls. To estimate relative risks (RR) associated with dietary and other variables, odds ratios were calculated (Breslow and Day, 1980), adjusted for age, sex, and ever/never smoked cigarettes, and tested for trend across ordered categories (Mantel, 1963). Additional adjustment for education and amount smoked had a minimal effect on any estimate of the odds ratio. Because of *a priori* suspicion that risks and exposure prevalences might differ between residents of northern (higher risk) communes where prevention campaigns had been launched in the 1970's and southern (lower risk) communes in Linxian, risk patterns were also examined separately in the 2 areas. In addition, risks for cancer of the esophagus and cardia, and for squamous-cell cancer and adenocarcinomas, were examined separately as well as in combination. Multivariate analysis was performed using multiple logistic regression (Breslow and Day, 1980).

RESULTS

Interviews were completed for each of the 1,314 controls selected and for 1,244 cases (98.3% of all patients identified). Nearly all (94.2%) of the controls and the majority (79.3%) of the cases were interviewed at home. Approximately 10% of cases were interviewed in the hospital, with most of the remaining interviews conducted at the subject's worksite. There were no proxy interviews, but a relative or neighbor assisted the subject in 4.3% of control interviews and 5.8% of case interviews. The median duration of the interview was 65 min, with a range of 20–140 min. Approximately one-third of the interviews were conducted in the presence of a spouse or other relative or friend of the study subject.

Age-adjusted (standardized to the world age distribution) EC incidence rates over the study period were 310 per 10^5 per year in the high-risk communes and 180 per 10^5 per year in the low-risk communes. These observed rates were slightly higher than those reported by the Linxian Cancer registry during the period 1959–1981 (Lu *et al.*, 1985).

Table I shows the distribution of the cancer cases according to anatomic location and histology of the tumors. Approximately one-third of the cancers occurred in the gastric cardia, with another 4% in both the cardia and esophagus. Among the 782 esophageal cancers, most (n = 462) were located in the middle third, with smaller numbers confined to the upper third only (n = 98) or lower third only (n = 114) or showing diffuse location throughout the esophagus (n = 108). Information on cell type was not available for the 52% of cases diagnosed only by X-ray (*i.e.*, barium meal). Among those with a histologic diagnosis, squamous-cell carcinomas predominated (96%) among tumors of the esophagus, while over 90% of the cardiac tumors were adenocarcinomas. The distributions of cell type and tumor location did not differ by sex, although the males did have a slightly higher proportion of cancer of the cardia than females.

TABLE I – ANATOMIC AND HISTOLOGIC DISTRIBUTION OF CANCER CASES

Histology	Tumor location				
	Esophagus	Cardia	Mixed	Unknown	Total (%)
Squamous-cell	338	18	8	7	571 (30)
Adenocarcinoma	10	194	10	0	214 (17)
Other	2	1	10	1	14 (1)
Unknown	432	184	26	3	645 (52)
Total (%)	782 (63)	397 (32)	54 (4)	11 (1)	1,244 (100)

Table II provides information on demographic and socioeconomic characteristics of the study subjects. Cases tended to be better educated than controls. The age distributions were generally similar, although cases were slightly younger on average. A total of 54% of the cases were residents of Linxian's northern communes, where rates of esophageal cancer have historically been highest, compared to 41% of the controls. Nearly all the participants lived most of their lives in Linxian.

Tobacco and alcohol

Virtually none of the women smoked cigarettes or drank alcoholic beverages. Only 28 men reported ever drinking alcoholic beverages at least once a month for 6 months or longer, with no excess consumption among cases. Among males more cases (61%) than controls (56%) were smokers, the average numbers of cigarettes smoked per day being 13.8 and 12.7, respectively. As shown in Table III, the risk of cancer of the esophagus and gastric cardia was higher among smokers, and rose with increasing amount smoked and with earlier age at

TABLE II – DEMOGRAPHIC AND SOCIAL CHARACTERISTICS OF STUDY SUBJECTS

Variable	Males		Females	
	Controls	Cases	Controls	Cases
Number of subjects	789	758	525	486
Age (yrs)	55.8 ± 6.4[1]	54.7 ± 6.7	55.7 ± 6.5	54.4 ± 6.8
<45	9%	11%	6%	7%
45–54	34%	35%	33%	29%
55–64	58%	54%	61%	64%
Years of education				
0	30%	29%	73%	71%
1–5	56%	52%	25%	26%
6+	14%	19%	2%	4%
Years lived outside Linxian				
0	48%	52%	83%	87%
1–9	33%	29%	11%	8%
10–19	12%	10%	5%	4%
20+	7%	9%	3%	1%

[1]Values represent mean ± standard deviation.

TABLE III – RELATIVE RISKS OF ESOPHAGEAL/GASTRIC CARDIA CANCER AMONG LINXIAN MALES ACCORDING TO CIGARETTE SMOKING

Smoking index	High-risk northern communes				Low-risk southern communes			
	Case	Control	RR	95% CI	Case	Control	RR	95% CI
Non-smoker	136	100	1.0	—	158	248	1.0	—
Smoker	256	224	0.9	0.6–1.2	208	217	1.5	1.1–2.0
Number/day								
1–9	57	50	1.0	0.6–1.6	70	79	1.4	0.4–2.1
10–19	79	76	0.8	0.5–1.2	56	66	1.3	0.9–2.0
20+	120	98	0.9	0.6–1.4	82	72	1.7	1.2–2.6
Age started								
<20	43	32	1.0	0.6–1.7	28	33	1.3	0.7–2.3
20–24	89	63	1.1	0.7–1.7	81	57	2.2	1.5–3.4
25–34	72	67	0.8	0.5–1.3	58	44	2.1	1.3–3.3
35+	52	62	0.7	0.4–1.1	41	83	0.8	0.5–1.2

RR adjusted for age.

starting in the low-risk communes, whereas little effect was seen in the high-risk communes. The smoking-associated risks in the low-risk southern communes were somewhat higher for cancers of the cardia than of the esophagus and for histologically than radiologically confirmed cases (Table IV). Our questionnaire also enquired about opium, which 99.4% of the subjects denied using.

Pickled vegetables

There was little or no evidence that increased EC risk was associated with increased intake of pickled vegetables (Table V) in either the southern, low-risk communes or the northern, high-risk communes. Reported changes with time were minimal in the northern communes, but residents of the low-risk communes reported more frequent use of pickled vegetables in the later time period. The overall reported prevalence of use was lower in the northern communes than in the southern ones, possibly as a result of education campaigns conducted in the north to reduce the consumption of pickled vegetables. There was no difference in the pattern of EC risk during the 2 time periods in either group of communes, nor did risk patterns vary by sex, even though females reported a higher intake than did males. Eliminating cases that were not histologically confirmed did not change these patterns, nor were there demonstrable differences between risks for tumors of the esophagus and cardia.

There also was no increase in risk associated with higher intake of moldy foods, including moldy pickled vegetables. The sprouting or molding of corn during storage, a sign of damp conditions that would foster mold on other foods, was associated with slightly increased risk, but very few subjects reported this occurrence.

Other dietary items

Grains, vegetables and legumes were the most commonly eaten foods in Linxian, whereas animal foods (meat, eggs, poultry) and fruits were seldom consumed during either the 1970's or the 1950's. Table VI shows that higher overall intake of staple foods was associated with slightly increased cancer risk, due to higher risks seen in the highest quartiles of wheat and corn intake, while risks were unrelated to sweet potato intake and were lower in the higher quartiles of millet consumption. The trend with wheat consumption was most pronounced, with cancer risks twice as high among those in the highest compared to lowest quartiles of intake. High consumption of animal foods was also associated with significantly increased risk of cancer of esophagus/cardia, but most individuals ate these foods only monthly or less frequently.

High intake of dried vegetables was associated with slightly decreased risk of esophageal/cardiac cancer, whereas intake above the first quartile of the nutritionally "better" fresh vegetables was associated with a 40–50% increased risk. A similar pattern was seen for cruciferous (*Brassica* family) vegetables (cabbages, turnips), and a slight increase was linked to higher legume intake. No specific relationship with risk of esophageal/cardiac cancer was found with intake of vegetables of the *Allium* family (garlic, onion, chives, scallions). There was also little or no association with fresh fruit consumption. None of the odds ratios associated with these dietary variables varied greatly by commune, tumor location, or histology. To examine whether the univariate dietary effects shown in Table VI were due to confounding with other dietary covariates, we constructed a multivariate logistic regression model that simultaneously adjusted for age, sex, smoking, hot and cold beverage consumption and the variables in Table VI that showed evidence of association. Positive associations of EC risk with corn and fresh vegetables were reduced in magnitude and confined to the second quartile of intake in the multivariate analysis. The protective effects of millet, hot water and cold water persisted, however, as did the positive association with total staples, particularly wheat. The effects of legumes, animal products and dried vegetables were no longer statistically significant.

Use of vitamin pills was uncommon, reported by only 2% of cases and 4% of controls among males, and 3% of cases and 5% of controls among females.

TABLE IV – RELATIVE RISKS OF CANCER AMONG MALE SMOKERS ACCORDING TO ANATOMIC TUMOR LOCATION AND HISTOLOGIC CONFIRMATION

Tumor location	Histologic confirmation	High-risk northern communes		Low-risk southern communes	
		RR	95% CI	RR	95% CI
Esophagus	Yes	0.8	0.5–1.3	1.7	1.0–3.0
	No	0.8	0.5–1.3	1.2	0.8–1.7
	Total	0.8	0.6–1.3	1.3	0.9–1.8
Cardia	Yes	0.9	0.5–1.6	2.0	1.2–3.5
	No	1.5	0.7–3.3	1.3	0.8–2.0
	Total	1.1	0.7–1.7	1.6	1.1–2.3

RR adjusted for age.

Beverages and water supply

There was little or no association between cancer risk and frequency of intake or temperature of beverages. Teas of any kind were rarely consumed, and we detected no elevated risk of esophageal/cardiac cancer associated with high-tannin foods overall (*i.e.*, tea and persimmons). Plain hot or cold water was more frequently consumed than other beverages, especially in the 1970's, but many subjects reported never even consuming water. For the later time period, significant decreases in cancer risk were found for subjects drinking hot (RR = 0.8, 95%

TABLE V – RELATIVE RISKS OF ESOPHAGEAL/GASTRIC CARDIA CANCER ASSOCIATED WITH CONSUMPTION OF PICKLED VEGETABLES

	Pickled vegetable intake	Higher risk northern communes				Lower risk southern communes			
		Cases	Controls	RR	95% CI	Cases	Controls	RR	95% CI
Males	In 1970's								
	Never	236	174	1.0	—	85	73	1.0	—
	Up to once/day	63	73	0.6	0.4–0.9	68	119	0.5	0.3–0.8
	More than once/day	91	77	0.9	0.6–1.3	210	273	0.8	0.5–1.1
	In 1950's								
	Never	204	170	1.0	—	114	144	1.0	—
	Up to once/day	84	71	1.0	0.7–1.5	81	135	0.8	0.5–1.8
	More than once/day	102	82	1.0	0.7–1.6	168	185	1.2	0.9–1.8
Females	In 1970's								
	Never	121	96	1.0	—	20	28	1.0	—
	Up to once/day	55	45	0.9	0.5–1.5	43	67	0.9	0.4–1.9
	More than once/day	101	71	1.1	0.7–1.7	144	216	0.9	0.5–1.8
	In 1950's								
	Never	107	81	1.0	—	52	70	1.0	—
	Up to once/day	70	56	0.9	0.6–1.5	42	84	0.7	0.4–1.2
	More than once/day	100	77	1.0	0.7–1.6	112	156	0.9	0.6–1.5

RR adjusted for age and (for males) smoking.

CI = 0.6–0.9) or cold (RR = 0.8, 95% CI = 0.6–0.9,) water on an occasional or daily basis, compared to never.

No consistent increase in risk was associated with use of any particular type of water supply during either time period. The odds ratio was increased to 1.2 in subjects reporting that they cleaned their water vessels monthly, rather than weekly, but this was significant only for the late 1950's.

Height and weight

The cancer patients were slightly taller and heavier (by self-reported height and weight 5 years prior to interview). The mean heights for cases and controls, respectively, were 167 *vs.* 166 cm among males, 157 *vs.* 156 cm among females. The mean weights were 53 *vs.* 51 kg for males, 44 *vs.* 44 kg for females.

Familial cancer

More cases than controls reported a family history of cancer (Table VII). The increase in risk reached 70% for persons whose parent or parents had had esophageal or stomach cancers. The risk of having a spouse with cancer was slightly (RR = 1.2) but not significantly increased. Over 90% of the cancers in family members were reported as esophageal or stomach cancers.

Occupation

Almost all the subjects in this rural county had worked on farms, farming being reported as the current occupation for 89% of males and 71% of females. These percentages were somewhat higher for controls than for cases. The most common crops were wheat, corn, sweet potatoes and millet, in the 1950's as well as more recently. Almost all persons used chemical fertilizers as well as the more traditional compost and "night soil".

DISCUSSION

This study was initiated to test several plausible hypotheses regarding the causes of esophageal and gastric cardia cancer in Linxian. Despite a large sample size, detailed assessments of many exposures, and apparent variation in exposures among the subjects, we were unable to identify any single strong environmental or dietary risk factor that could account for the exceptionally high esophageal or cardiac cancer rates in Linxian. Little relationship was observed between cancer risk among Linxian residents and intake of pickled vegetables, even though pickled vegetables are more commonly eaten in Linxian than elsewhere, and a geographic (ecologic) correlation has been shown between esophageal cancer mortality and pickled vegetable intake among communes in several provinces in China (Yang, 1980). Our results were surprising, given that extracts of pickled vegetables are mutagenic according to the Ames test; that fermentation associated with the pickling enhances the formation of specific nitrosamines and N-nitroso compounds, which have been detected in pickled vegetable samples; and that tumors of the forestomach have been induced in rats fed food inoculated with a type of mold (*Fusarium*) often found in pickled vegetables (Li and Cheng, 1986).

We also did not observe a lower risk among persons consuming more fresh vegetables, as seen in several studies of esophageal cancer in western countries and among Chinese in Singapore (Mettlin *et al.*, 1981; Ziegler *et al.*, 1981; Tuyns *et al.*, 1987; De Carli *et al.*, 1987; de Jong *et al.*, 1974). In fact, "better" diet was associated with slightly but significantly higher risk of esophageal/cardiac cancer, as were several other indicators of higher income. Adjustment for education, a presumed surrogate for economic status, did not eliminate these small increases in risk. Higher intake of millet, previously found to be contaminated with silica fragments (O'Neill *et al.*, 1982), was also not confirmed as a risk factor. We did detect a fairly strong trend of increasing risk with rising wheat consumption. Although wheat consumption was not proposed as a major risk factor before the study, it is noteworthy that this grain is a staple in other areas of the world where esophageal cancer is common, including Iran where *per capita* bread intake is twice as high in high- as in low-risk areas (Joint Iran-IARC Group, 1977; Cook-Mozaffari *et al.*, 1979; van Rensburg *et al.*, 1981). High wheat and corn consumption have also been linked to the clustering of esophageal cancer in South Africa, with a recent case-control study among Zulu men showing a stronger association for maize meal than any other factor (van Rensburg *et al.*, 1983*a*,*b*).

There was an increase in risk associated with lower fluid intake, with cases consuming both less hot and less cold water. Intake of liquids seemed very low even among controls. The finding is consistent with ecological evidence, which shows that clusters of high rates of esophageal cancer around the world tend to occur in dry, infertile areas (van Rensburg *et al.*, 1981). Linxian itself had been subject to periodic droughts, and water historically had been in limited supply prior to the 1960's, when an extensive irrigation system was introduced. It

TABLE VI – RELATIVE RISKS OF ESOPHAGEAL/GASTRIC CARDIAC CANCER ASSOCIATED WITH YEARLY INTAKE OF VARIOUS FOODS DURING THE LATE 1970's

Food group	Times/yr[1]	Cases	Controls	RR[2]	95% CI
Total staples (corn, wheat, millet, sweet potato, rice)	<712	243	328	1.0	—
	713–907	284	329	1.2	0.9–1.5
	908–1,132	395	328	1.6	1.3–2.0
	>1,132	322	328	1.4	1.1–1.7
Wheat	<48	206	330	1.0	—
	48–91	257	324	1.2	0.9–1.5
	91–183	352	332	1.6	1.3–2.1
	>183	429	328	2.0	1.5–2.5
Corn	<21	238	330	1.0	—
	24–185	343	328	1.4	1.1–1.8
	186–367	362	322	1.3	1.0–1.6
	>367	361	334	1.5	1.2–1.9
Millet	<115	426	328	1.0	—
	115–235	280	329	0.7	0.5–0.8
	244–365	289	380	0.6	0.5–0.8
	>365	249	277	0.7	0.6–0.9
Sweet potatoes	<175	342	338	1.0	—
	176–265	294	312	0.9	0.7–1.2
	266–366	310	346	0.9	0.7–1.1
	>367	298	317	1.0	0.8–1.2
Fresh vegetables	<483	229	327	1.0	—
	483–714	350	329	1.5	1.2–1.9
	718–973	321	328	1.4	1.1–1.7
	>973	343	327	1.5	1.2–1.9
Dried vegetables	<30	332	331	1.0	—
	30–73	307	313	1.0	0.8–1.2
	74–117	356	349	1.0	0.8–1.3
	>117	249	321	0.8	0.6–1.0
Fresh fruit	0	352	413	1.0	—
	1–11	295	304	1.1	0.9–1.4
	12–35	311	288	1.2	0.9–1.5
	>35	284	306	1.0	0.8–1.2
Legumes, nuts, seeds	<14	253	335	1.0	—
	14–47	286	323	1.2	0.9–1.5
	48–122	376	324	1.5	1.2–1.9
	>122	328	330	1.3	1.0–1.6
Meat, poultry, eggs, fish	<3	297	389	1.0	—
	3–15	568	607	1.6	0.9–1.5
	>15	378	316	1.5	1.2–1.9

[1]Yearly frequency of intake of male controls.–[2]RR adjusted for age, sex and smoking.

is possible that very low fluid consumption may render the esophagus and cardia susceptible to physical or chemical injury from other sources, such as a dry, coarse diet. Indeed, low water and high wheat intake combined to increase risk more than 3-fold in our study.

We did not find that the source of water used in the home was related to risk, nor were storage methods, except for a slightly elevated risk among those who stored their water for longer periods of time. Prior surveys have revealed higher concentrations of nitrates in drinking water in brigades of Linxian with higher esophageal cancer mortality rates (Yang, 1980), and levels of nitrate and several nitrosamino acids were higher in urine specimens from residents of Linxian than in a neighboring low-risk area (Lu *et al.*, 1986). In this study we did not measure concentrations of nitrate, nitrite or other compounds in water supplies, nor perform any environmental or food sampling for nitrosamines or other carcinogens in the homes of the subjects.

A higher risk of esophageal and of cardiac cancer was found among smokers in southern but not northern communes. Smoking does not represent the major cause of cancer in Linxian, where hardly any women smoke cigarettes and amounts smoked by men are low by western standards. Nevertheless, sex-specific differences in smoking prevalence may contribute to the higher rates (1.6-fold) among males in Linxian. (In our case series the male:female ratio was 1.3 for esophageal cancer and 2.5 for cardiac cancer.) The excess risk observed among smokers in this study is comparable with the moderate (about 50% or so) excess risks observed for stomach cancer in several large cohort studies of smokers in other countries (Surgeon General, 1982), as well as in a recent case-control study in Shandong Province, China (You *et al.*, 1988). Virtually none of the subjects reported consumption of alcohol. The absence of alcohol drinking also probably reduces the impact of smoking, since smoking and drinking appear in other studies to combine in a multiplicative fashion to cause esophageal cancer (Surgeon General, 1982).

A positive family history of esophageal or cardiac cancer was a significant risk factor. Familial clustering of esophageal cancer has also been reported in nearby Shanxi Province (Li and He, 1985). In a society like that of Linxian, members of a family live and eat in close proximity and inevitably share environmental as well as genetic factors. The possibility of a genetic component is suggested by the higher risk associated with having a parent, and to some extent a sibling, than a spouse with cancer, although this differential could also indi-

TABLE VII – RELATIVE RISKS OF ESOPHAGEAL/GASTRIC CARDIA CANCER ASSOCIATED WITH A HISTORY OF CANCER IN FAMILY MEMBERS

	Cases	Control	RR	95% CI
Mother or father had cancer				
No	808	998	1.0	—
Esophageal/ stomach cancer	420	301	1.7	1.4–2.0
Other cancer	16	15	1.2	0.6–2.7
Sibling had cancer				
No	986	1,076	1.0	—
Esophageal/ stomach cancer	243	217	1.4	1.1–1.7
Other cancer	15	21	0.8	0.4–1.6
Spouse had cancer				
No	1,193	1,264	1.0	—
Esophageal/ stomach cancer	46	45	1.2	0.8–2.0
Other cancer	5	5	1.1	0.3–4.4

RR adjusted for age, sex and smoking.

cate the importance of exposures early in life. Genetic susceptibility has been suggested by an increased frequency of blood group A among esophageal (but not cardiac) cancer patients in a previous survey in Linxian (Wu *et al.*, 1981). Despite familial aggregation in various high-risk areas, genetic predisposition has not been thought to be a major contributor to esophageal cancer (Day and Muñoz, 1982).

Of note in our investigation is the assembly of the largest number of gastric cardia cases available for etiologic study. About one-third of the cancer patients had cardiac rather than esophageal cancer. One consequence of this observation is that the rates of incidence and mortality from esophageal cancer previously reported from Linxian are about one-third too high. On the other hand, the rates reported for stomach cancer are too low, and the rates for cardiac cancer (approximately 50 and 30 per 10^5 in males and females) are among the highest in the world. In populations having high rates of stomach cancer, tumors of the gastric cardia usually comprise only a small fraction of all gastric cancers. The associations with the dietary and other variables in our study were similar for esophageal and cardiac cancer, despite the different cell types at these anatomic locations.

There are several possible explanations for our inability to detect environmental risk factors that might account for a 10-fold increase in esophageal cancer in Linxian compared to the rest of China:

(1) There may be an insufficient variation in exposures among the study subjects, which would reduce statistical power. We found, however, considerable variation in responses to most of the questions asked. For example, 29% of the cases in the high-risk communes reported more than daily consumption of pickled vegetables in the 1970's, whereas 54% reported no consumption at all. Much of the range of intake of various nutrients in Linxian, however, may fall below the threshold of any protective dose-response relationship which would be observed in a Western population. Deficiencies of many vitamins, particularly riboflavin, ascorbic acid, folic acid, vitamin A and vitamin E, as well as extraordinarily low fat intake, affect a high percentage of the Linxian population (Yang *et al.*, 1982; Thurnham *et al.*, 1985; Zheng *et al.*, in press), so that even the highest quartiles of intake appear unsatisfactory by accepted criteria of an adequate diet (NRC, 1980). This is supported by data from 24-hr dietary recall interviews conducted with 347 individuals as part of an ongoing nutrition monitoring program in Linxian, which found deficient diets in a large proportion of subjects (data not shown).

(2) We did not inquire about exposures during childhood, which may be relevant to esophageal/cardiac cancer etiology. Effects of exposures at young ages would have been detected only if they were highly correlated with exposure in adult life.

(3) As in all studies of diet and chronic disease, misclassification of exposure undoubtedly occurred in this study. Random misclassification alone cannot change the direction of an effect, but differential misclassification concerning cases vis-à-vis controls could. Extensive mass education campaigns in the northern communes in the late 1970's discouraged the population from eating pickled vegetables, so that cases, who may be stigmatized by their diagnosis, may have selectively underestimated or underreported their intake. However, we found no effect of pickled vegetable consumption in the 1950's in the northern communes or in either time period in the southern, low-risk communes. In addition, using unpublished data from an ongoing intervention trial in Linxian, we found no case-control differences in pickled vegetable intake ascertained before entry into the trial, arguing against differential recall by cases. Our case-control interview data are also qualitatively in accord with limited historical data on county agricultural production, which show that the frequency of intake of meat, vegetables, wheat and rice was higher in the 1970's than in the 1950's.

(4) Misclassification of disease status may have masked real effects. Although it is unlikely that a condition resulting in progressive difficulty in swallowing, presenting with an esophageal or cardiac mass detectable by X-ray and usually fatal, would not be cancer, we were concerned that histologic confirmation of the diagnosis was only available for just under half the patients. About one-third of the cases had cancers of the gastric cardia rather than of the esophagus, and the case series represented a mixture of squamous-cell carcinomas and adenocarcinomas of possibly different etiologies. The combining of esophageal and cardiac cancers in this study, however, seemed to have little influence on the study results and patterns were similar for histologically confirmed and unconfirmed cases.

(5) Selection bias may have occurred. The patients in this study may represent a subset of the population more likely to receive prompt medical care or otherwise be more privileged (as suggested by their slightly better diets and education as well as greater height and weight). Such a selection bias seems unlikely to be severe, since the cancer ascertainment system covered all of Linxian fairly thoroughly. To limit this possibility, our study excluded persons over age 65, who are less likely to seek diagnostic checkups and hospital care.

(6) The control group may have included a high percentage of individuals with esophageal abnormalities, whose risk factors may be similar to those for cancer. Prior cytologic screening surveys in Linxian have revealed that the majority of the population is affected by chronic esophagitis, with esophageal dysplasia affecting up to 20% of adults (Li, 1982; Muñoz *et al.*, 1982). If the effect of diet on esophageal cancer risk is similar to its effect on esophageal abnormalities, both protective and causal relationships would be masked by including a large proportion of persons with these abnormalities in the control group.

(7) Finally, we may not have inquired about the environmental exposure or exposures causing most of the cancers in Linxian. Conversely, the specific agents may not be detectable by traditional epidemiologic approaches.

In summary, this study attempted to explain the extraordinarily high levels of esophageal/cardiac cancer in Linxian by looking for differential rates of exposure of persons with cancer compared to those without. No single dominant environmental factor was identified, but our data suggest that several hypothesized exposures, particularly to pickled vegetables, are not likely to be responsible for the high cancer rates. If the rate of esophageal cancer in Linxian is 10 times higher than in com-

parable regions, the relative risk for exposed *versus* unexposed within Linxian county would have to be considerably greater than 10. It seems unlikely that any shortcomings of this study could mask such a strong effect.

The reason for the extremely high esophageal cancer rates in Linxian thus remains enigmatic, although the associations with low fluid and high wheat intake are intriguing. Similarly, in the high-risk areas of Iran bordering the Caspian Sea, where use of opium pipe residues and poor nutrition have been implicated, the case-control approach has yielded only limited insight into the determinants of esophageal cancer (Joint Iran-IARC Group, 1977; Cook-Mozaffari *et al.*, 1979; Day and Muñoz, 1982; Ghadirian *et al.*, 1985). Further clues to the etiology of cancer of the esophagus and gastric cardia in Linxian may come from ongoing randomized controlled trials testing the influence of specific nutrients on cancer risk (Blot and Li, 1985).

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